SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

DEVICE GENERIC NAME:	Absorbable Adhesion Barrier
DEVICE TRADE NAME:	GYNECARE INTERGEL Adhesion Prevention Solution
APPLICANT:	Lifecore Biomedical, Inc. 3515 Lyman Boulevard Chaska, MN 55318-3051
PREMARKET APPROVAL APPLICATION (PMA):	P990015
DATES OF PANEL RECOMMENDATIONS:	January 12, 2000 & September 6, 2001
DATE OF GMP INSPECTION:	December 28, 1999 & January 14, 2000
DATE OF NOTICE OF APPROVAL OF APPLICATION:	
EXPEDITED REVIEW:	Expedited processing was authorized on April 26, 1999, based on the potential of GYNECARE INTERGEL to provide a specific public health benefit by reducing the incidence, extent, and severity of newly formed adhesions.

II. INTENDED USE/INDICATIONS

GYNECARE INTERGEL Solution is indicated for use in patients undergoing open, conservative gynecologic surgery as an adjunct to good surgical technique to reduce post-surgical adhesions. GYNECARE INTERGEL Solution is also intended to reduce the likelihood of developing moderate or severe postoperative adnexal adhesions in these patients.

III. DEVICE DESCRIPTION

GYNECARE INTERGEL Solution is a sterile, nonpyrogenic, amber colored, viscous solution of sodium hyaluronate, which has been ionically crosslinked with ferric ions and

provides a transient viscous, lubricious coating on the peritoneal surfaces following surgical procedures.

GYNECARE INTERGEL Solution is packaged in a 300 mL low density polyethylene bellows-type bottle, which is provided sterile in a plastic tray using a Tyvek® lid. When stored at refrigerated (2-8 °C) or controlled room temperature (15 - 30°C), INTERGEL has a stable shelf life of 24 months.

IV. CONTRAINDICATIONS

GYNECARE INTERGEL Solution is contraindicated in patients with pelvic or abdominal infection.

V. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the GYNECARE INTERGEL Solution labeling, which is available on the FDA web site at *http://www.fda.gov/cdrh/pdf/p990015.pdf.*

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Practices intended to minimize adhesion formation include good surgical technique with attention to gentle and minimal tissue handling, meticulous hemostasis and avoidance of foreign particles, e.g., talc, lint, and use of adjuvants such as crystalloid solutions. Alternative devices approved as adjuncts intended to reduce adhesions include INTERCEED (TC7) Absorbable Adhesion Barrier (Ethicon, Inc.) and SEPRAFILM Bioresorbable Membrane (Genzyme Corp.)

VII. ADVERSE EFFECTS

Table 1 reports the local (surgical site) adverse events observed in patients treated with INTERGEL Solution during an international, randomized, double-masked, multi-center study comparing the safety and effectiveness of GYNECARE INTERGEL Solution (300 mL) and lactated Ringer's solution (300 mL) in 281 patients (GYNECARE INTERGEL Solution: 143 patients; lactated Ringer's solution: 138 patients).

Table 1: Local (Surgical Site) Adverse Events

	Intergel		Control	
# Patients Enrolled	143		138	
Incision inflammation	8	(5.6%)	8	(5.8%)
Incision opening	7	(4.9%)	5	(3.6%)
Pain:				
Incisional	9	(6.3%)	13	(9.4%)
Abdominal	39	(27.3%)	42	(30.4%)
Pelvic	3	(2.1%)	3	(2.2%)
Back	13	(9.1%)	7	(5.1%)
Infection:	8[a]	(5.6%)	4[b]	(2.9%)
Possibly device related (Investigator assessment)	3[c]	(2.1%)	1[d]	(0.7%)

[a] bladder; wound(2); pelvic/wound; unspecified(2); chlamydia; vaginal

[b] wound(2); unspecified; vaginal

[c] bladder; pelvic/wound; unspecified

[d] wound

Table 2 reports systemic adverse events observed in 5% or more of the study patients.

Table 2: Systemic Adverse Events Reported Greater than 5%, Number (%) of Patients

Body System Preferred Term	INTERGEL (N=143)		lactated Ringer's Solution (N=138)	
Body as a Whole	**143**	**(100)**	**137**	**(99.3)**
Pain	122	(85.3)	111	(80.4)
Headache	45	(31.5)	37	(26.8)
Fever	25	(17.5)	19	(13.8)
Allergic reaction	3	(2.1)*	10	(7.2)
Digestive	**106**	**(74.1)**	**100**	**(72.5)**
Nausea	66	(42.6)	65	(47.1)
Constipation	47	(32.9)	56	(40.6)
Flatulence	35	(24.5)	35	(25.4)
Vomiting	13	(9.1)	14	(10.1)
Dyspepsia	14	(9.8)	10	(7.2)
Urogenital	**44**	**(30.8)**	**40**	**(29.0)**
Dysmenorrhea	25	(17.5)	22	(15.9)
Nervous	**37**	**(25.9)**	**40**	**(29.0)**
Insomnia	20	(14.0)	22	(15.9)
Dizziness	15	(10.5)	13	(9.4)
Respiratory	**30**	**(21.0)**	**26**	**(18.8)**
Cough, increased	11	(7.7)	8	(5.8)
Rhinitis	8	(5.6)	7	(5.1)
Cardiovascular	**15**	**(10.5)**	**15**	**(10.9)**
Tachycardia	4	(2.8)	7	(5.1)
Hemic and Lymphatic	**19**	**(13.3)**	**16**	**(11.6)**
Anemia	12	(8.4)	13	(9.4)
Skin	**13**	**(9.1)**	**13**	**(9.4)**
Pruritus	8	(5.6)	10	(7.2)

*p = 0.048, Fisher's Exact test.

In one randomized non-blinded laparoscopy trial of patients in the United States (221 subjects), wound infections were reported for 5 GYNECARE INTERGEL Solution patients (4.4%) and no patients (0.0%) in the control group (lactated Ringer's solution). There was one report of a possible, post-operative pelvic infection in the control group (1.0%). In a similar randomized non-blinded laparoscopy trial in Europe (144 patients), there were 5 reports of possible, post-operative pelvic infection (6.8%) in the GYNECARE INTERGEL Solution patients, and one report(1.4%) in the control group.

VIII. MARKETING HISTORY

GYNECARE INTERGEL Solution has been marketed in Europe, Canada, the Middle East and South Africa since 1998.

GYNECARE INTERGEL Solution has not been withdrawn from the market for any reason related to the safety or effectiveness of the product.

IX. SUMMARY OF PRECLINICAL STUDIES

Biocompatibility and Toxicology Studies:
Safety studies conducted in support of the safety of GYNECARE INTERGEL Adhesion Prevention Solution included both standard biocompatibility studies and product specific toxicology studies.

Biocompatibility Studies:
The biocompatibility studies performed in support of the safety of GYNECARE INTERGEL Solution were *In Vitro* Cytotoxicity, Dermal Sensitization, Pyrogenicity and Hemolysis. No cytotoxicity, dermal sensitization, pyrogenicity nor hemolysis were detected in any of these studies. These studies demonstrated that GYNECARE INTERGEL Solution is not cytotoxic, not a dermal sensitizer, not pyrogenic and not hemolytic under the conditions of the studies performed.

***In Vivo* Acute Toxicity:**
Seven acute toxicity studies were conducted with GYNECARE INTERGEL Solution administered intraperitoneally (i.p.) using Swiss-Webster mice, Fischer rats, New Zealand White rabbits, and Beagle dogs. In the acute toxicity studies, GYNECARE INTERGEL did not produce significant treatment-related clinical signs of toxicity, effects on body weight or weight gain, or gross lesions following intraperitoneal administration at dose volumes up to 20 mL/kg in sexually immature Fischer 344 rats, 50 mL/kg in Beagle dogs, 100 mL/kg in Swiss-Webster mice and sexually mature Fischer 344 rats, and 150 mL/kg in New Zealand White rabbits.

One Beagle dog exhibited transient, systemic toxicity following i.p. administration of 100 mL/kg GYNECARE INTERGEL Solution and clinical signs of toxicity and mortality were observed at dose volume of 150 mL/kg in Swiss-Webster mice and sexually immature Fischer 344 rats. Transient reduction in food consumption and fecal output, effects on body weights and weight gains, changes in various clinical pathology parameters (only at the high dose), and granulomatous peritonitis were also observed in sexually immature Fischer 344 rats following i.p. administration at dose volumes from 30 to 100 mL/kg GYNECARE INTERGEL Solution. The adverse systemic toxicity in the sexually immature Fischer 344 rats appears to be idiosyncratic, especially since older rats of the same strain and in one study, the same batch, did not experience the same toxicity or constellation of gross lesions associated with the peritonitis.

The highest dose of GYNECARE INTERGEL Solution that did not cause any toxicity was 25 ml/kg (in sexually immature Fischer 344 rats). This dose is 5 times higher than the recommended clinical instillate of 5 ml/kg.

Multiple-Dose Sub-Chronic Toxicity:
The toxicity of GYNECARE INTERGEL Solution following repeated dose administration was evaluated using Beagle dogs. In the multiple dose toxicity studies, no mortality occurred in animals injected i.p. with GYNECARE INTERGEL Solution at dose volumes up to 15 mL/kg/dose every third day for 28 days. There were no treatment-related differences in

clinical pathology (i.e. hematology, coagulation, blood chemistry and urinalysis) or in organ weights. The only treatment-related changes apparent upon gross or microscopic examination consisted of an accumulation of an iron-containing residue of the formulation in the lymph nodes draining the abdominal cavity, in mesothelial cells covering the abdominal viscera and/or in macrophages in the omentum or on the serosal surface of the abdominal and pelvic viscera. No evidence of systemic toxicity was observed in dogs from repeated intraperitoneal injection of GYNECARE INTERGEL Solution at dosage levels of 5, 10 and 15 mL/kg/dose.

Reproductive Toxicity:
The potential toxic effects of GYNECARE INTERGEL Solution on reproductive capabilities were evaluated using female Sprague-Dawley rats. The studies were designed to evaluate F0 estrous cycles, mating, conception, parturition, lactation and weaning, as well as F1 survival, growth and development.

In the fertility and general reproductive toxicity study of GYNECARE INTERGEL Solution in rats, dose volumes of 5, 15, and 25 mL/kg given i.p. every third day beginning 19 days prior to cohabitation until gestation day 6 produced no treatment-related effects on fertility or reproductive parameters, except for slight to significant reductions in the mean number of implantation sites and viable fetuses depending upon the volume of GYNECARE INTERGEL Solution administered. In a subsequent study, this effect was significantly reduced when dosing with GYNECARE INTERGEL Solution (25 mL/kg/dose) was stopped one day prior to cohabitation and eliminated when dosing was stopped seven days prior to cohabitation.

Conclusions of Toxicity and Biocompatibility Testing:
The toxicity and biocompatibility studies conducted with GYNECARE INTERGEL Solution demonstrated that this device is non-cytotoxic, non-toxic in mice, rats, rabbits, and dogs *in vivo* acutely and sub-chronically, non-hemolytic in rabbit blood, non-pyrogenic in rabbits, non-sensitizing in guinea pigs and non-toxic to fertility and reproductive parameters when the dosing interval was considered.

Preclinical Effectiveness Studies:

Numerous studies were performed to determine the formulation of GYNECARE INTERGEL Solution, using primarily the rabbit uterine horn simple abrasion model and the rabbit cecal/large bowel/sidewall abrasion model. When instilled prior to closing the abdomen, GYNECARE INTERGEL Solution was found to reduce adhesion formation in both of these model systems. ($p<0.05$).

GYNECARE INTERGEL Solution was tested against a low viscosity hyaluronic acid (HA) formulation in the rabbit cecal/large bowel/sidewall abrasion model. Animals received 15 mL of GYNECARE INTERGEL Solution or HA; those in the surgical group did not receive any treatment. Adhesions were evaluated seven (±1) days later. Adhesions to the sidewall were prevented in all animals treated with GYNECARE INTERGEL Solution (N=6); whereas in animals treated with HA, 40% of the sidewall was involved in adhesions compared with 66% in control animals. The number of sidewalls with no adhesions was also

evaluated. GYNECARE INTERGEL Solution completely prevented adhesions to all sidewalls (6 of 6 animals), whereas HA completely prevented adhesions to the sidewall in 2 of 7 animals, compared to 0 of 7 control animals.

Effects on Wound Healing:

The effects of GYNECARE INTERGEL Solution on colonic anastomosis and incision line wound healing were evaluated in female Long-Evans rats. In this study, the ascending colon was transected at a point approximately 2.5 cm aboral to the ileocecal junction and the transected ends were anastomosed with plain gut suture. Either 15 mL/kg saline, 5 mL/kg or 15 ml/kg GYNECARE INTERGEL Solution were applied to the colonic anastomosis and adjacent peritoneum. A fourth group of animals served as the sham controls and did not receive any treatment except for surgery. The final analysis of the study results demonstrated that intraperitoneal administration of GYNECARE INTERGEL Solution at dose volumes up to 15 mL/kg following surgery did not adversely affect healing of colonic anastomoses or incisional wounds in rats.

Effects on Infection Potentiation

The ability of GYNECARE INTERGEL Solution to potentiate infections caused by implantation of fecal material into the abdomen was evaluated in female Sprague-Dawley rats. Animals were divided, 20 per group, among the surgical control group, Ringer's Lactate High Dose (15 ml/kg) or Low Dose (5 ml/kg), and GYNECARE INTERGEL Solution High Dose (15 ml/kg) or Low Dose (5 ml/kg). The mortality rate was5/20 for the control animals, 3/20 for the Ringer's Lactate Low Dose and 5/20 for the High Dose and the mortality rate was 5/20 for the GYNECARE INTERGEL Low Dose and 9/20 for the High Dose. No significant differences in abscess scores for the liver, bowel, omentum, or "Other" sites were observed between any of the treatment groups. In contrast, treatment with GYNECARE INTERGEL Solution produced decreases in abscesses in the abdominal wall and in total abscess formation relative to the surgical control group. The low dose GYNECARE INTERGEL Solution group also had a lower total abscess score than the low dose Ringer's Lactate control group. The results of this study demonstrate that intraperitoneal administration of GYNECARE INTERGEL Solution at dose volumes up to 15 mL/kg results in increased deaths attributed to infection than similar doses of Ringer's lactate, but also results in lower abscess score than similar doses of Ringer's lactate.

This study was repeated using a model of mixed bacterial flora with a larger group of animals, powered to detect a difference between LD_{50} and LD_{75} at the clinical dose of 5ml/kg. In this study, no difference on mortality or abscess formation was observed in animals treated with lactated Ringer's solution compared with GYNECARE INTERGEL Solution.

Absorption, Distribution, and Excretion Studies

Several exploratory absorption, distribution, and excretion studies were conducted in rats, dogs and monkeys in which serum levels of HA and iron were determined following i.p. administration of GYNECARE INTERGEL Solution. These studies demonstrated that slight increases in serum iron were observed within the first 24 to 48 hours following dose

administration. Serum HA concentrations were shown to increase relative to GYNECARE INTERGEL Solution administered intraperitoneally The elevated serum HA levels are transient and do not suggest accumulation at the clinical intended dose (5 mL/kg), or at doses up to 30 mL/kg. Serum HA concentrations consistently returned to near pre-dose HA levels within 7 days or earlier, depending on the does; the greater the dose, the longer the time required to return to pre-dose levels

Information from autoradiography study in rats demonstrated that the pattern, mechanism, and extent of absorption, distribution, metabolism, and elimination of exogenous HA from the i.p. administered ferric hyaluronate (FeHA) solution appears to be the same as exogenous HA administered as HA alone. The tissues responsible for endogenous HA clearance also appear to efficiently metabolize the exogenous HA. The only difference between the two formulations appears to be a slightly longer residence time at the site following i.p. administration of FeHA. The delay in absorption of FeHA relative to HA, from the peritoneal cavity is most probably due to the greater viscosity of the ionically crosslinked formulation. From these studies, it is estimated that GYNECARE INTERGEL Solution clearance from the peritoneum is approximately twice that of HA. The elimination half-life ($T_{1/2}$) of GYNECARE INTERGEL Solution in humans is expected to be approximately 51 hours.

Effectiveness of FeHA in Other Animal Models

Preclinical evaluations were conducted in three studies with a rat cecal/liver adhesion model, In each study abrasions were made by wiping the cecum with gauze until punctate bleeding developed. Three 8-mm lesions were created on each side of the abdominal wall by removing a layer of the peritoneum and transverse abdominal muscle with a stainless steel biopsy punch. All accessible surfaces of the liver were abraded by rubbing them with the wooden end of a sterile swab. The injured sites received one of various test solutions. Animals in the surgical control group did not receive any treatment. The sites were examined for the extent of adhesions 7 days later. In all cases, the GYNECARE INTERGEL Solution-treated groups had significantly ($p<0.05$) reduced adhesions to the cecum and the liver lobes compared with the control group.

Stability Studies:

Stability studies were completed to support the shelf life of the product using the bellow packaging configuration. The results of the testing demonstrated that GYNECARE INTERGEL Solution has a shelf-life of 24 months when stored at 15 - 30° or 2-8°C.

X. SUMMARY OF CLINICAL EVALUATIONS

GYNECARE INTERGEL Solution has been studied in a pilot study and pivotal study in female patients undergoing peritoneal cavity surgery by laparotomy with a planned second-look laparoscopy. The purpose of these studies was to evaluate the safety and effectiveness of the device in reducing post-surgical adhesions. Patients were administered 300 mL of

GYNECARE INTERGEL Solution or lactated Ringer's Solution as an intraperitoneal instillate at the completion of the laparotomy procedure. Adhesions were assessed at prospectively determined anatomic sites, using prospective scales for extent and severity, before and after adhesiolysis at baseline laparotomy, and at second look laparoscopy. Safety was assessed based on adverse events recorded throughout the study, on clinical laboratory tests performed at baseline and post-therapy, and on gross evaluation at second-look.

PILOT STUDY

The pilot study was a randomized, unmasked, single investigator / single center trial of 23 patients to evaluate the preliminary safety and use of 300cc INTERGEL Solution compared to 300cc lactated Ringers control in female patients undergoing laparotomy for infertility. The pilot study enrolled 23 women, aged eighteen to forty-five year, undergoing limited, class 1 (clean), open peritoneal cavity surgery. The most common procedures were adhesiolysis and myomectomy performed for infertility. A total of 21 patients, 11 treatment and 10 control, completed the second look laparoscopy at 4 to 12 weeks after the initial surgery as part of the treatment plan. Eighteen pre-specified anatomic sites (Table 2) for adhesion incidence, extent and severity, as well as any other co-incident effects were evaluated during the second look laparoscopy. The mean incidence of baseline adhesions was 3.55 ± 4.52 for the 11 INTERGEL Solution patients and 4.33 ± 3.93 for the 9 control patients. (One control patient who had 17 adhesions at baseline, all of which reformed, was excluded from the analysis). At second look laparoscopy, the mean incidence of sites with adhesions was 6.09 ± 4.59 for the INTERGEL Solution patients and 11.00 ± 3.24 for the control patients ($p=0.015$). The safety profile was comparable for the 2 groups.

PIVOTAL STUDY

STUDY DESIGN

The pivotal study was designed to be a randomized, 12 center, 200 patient study to evaluate the safety and effectiveness of applying 300cc of Intergel compared to 300cc of Lactated Ringers at the end of clean (no gastro-intestinal or genito-urinary tract breach; no infectious process), peritoneal cavity laparotomy procedures.

The main criteria for inclusion in the study were:

- female patients 18 to 45 years of age requiring peritoneal cavity surgery via laparotomy with preservation of fertility
- patients scheduled for Day 7-28 post-surgical laboratory determinations
- patients who will be scheduled for a second-look laparoscopy as part of their treatment plan targeted for 6 to 12 weeks after the initial surgical procedure

The main preoperative criteria for exclusion in the study were:

- pregnant or lactating patients
- patients undergoing tubal sterilization, reversal of sterilization, or tubal implantation
- patients currently receiving cancer therapy including drugs and radiation
- patients who have lymphatic, hematologic or coagulation disorders, or patients taking coagulants
- patients with a history of hemochromatosis

- patients with hepatic or renal disorders
- patients who are taking oral or parenteral hypoglycemic agents for diabetes
- patients whose preoperative laboratory values are outside 20% of the normal range and are considered clinically significant
- patients who are immunocompromised or have autoimmune disorders
- patients who are unable to process large fluid loads, such as patients with congestive heart failure

The main intraoperative criteria for exclusion in the study were:
- patients with 12 or more of the 24 anatomical sites involved with adhesions
- patients receiving any peritoneal instillate containing corticosteroids, NSAIDs or Dextran
- patients in whom any absorbable hemostat is left in the abdominal/peritoneal cavity
- patients receiving any adhesion prevention adjuvant
- patients who will need postoperative hydrotubation
- patients presenting with pelvic or abdominal infection
- patients who will undergo peritoneal grafting as part of their postoperative procedure
- patients in who fibrin glue or other thrombogenic agents are used
- any surgical procedure at the time of the initial laparotomy that involves opening the gastrointestinal or urinary tract

TREATMENT PROTOCOL

Enrolled patients were otherwise healthy eighteen to forty-five year old women with limited adhesions (at less than twelve of twenty four sites), desiring to retain fertility, having no sites excised during first surgery and expecting to undergo second look laparoscopy as part of their treatment plan at 6 to 12weeks. During second look laparoscopy, twenty-four pre-specified anatomic sites (Table 3) were evaluated for adhesion incidence, severity and extent, as well as any other co-incident effects.

STUDY ENDPOINTS

The primary endpoint for effectiveness was Modified AFS score and the secondary effectiveness endpoints were the proportion of sites with adhesions, adhesion extent and adhesion severity. Safety was assessed based on adverse events recorded throughout the study, on clinical laboratory tests performed at baseline and post-therapy, and on gross evaluation at second-look.

Twenty-four abdomino-pelvic sites were evaluated for incidence (yes / no), severity (mild or severe) and extent of adhesions (<1/3; 1/3 to 2/3; >2/3). A composite score of 0 to 16 was determined per anatomic site based on adhesion incidence, severity and extent at each site. Scores per anatomic site (11 sites at first look; 24 sites at second look) were to be combined to determine an adhesion final score per patient.

Table 3: Anatomic Sites Evaluated

Pilot Study	Pivotal Study
Anterior peritoneum,	Caudal anterior peritoneum*
	Cephalad anterior peritoneum, right*
	Cephalad anterior peritoneum, left*
	Anterior peritoneum incision*
Small bowel,	Small bowel*
Omentum	Omentum*
Large bowel	Large bowel, right*
	Large bowel, left*
Anterior uterus,	Anterior uterus,
Posterior uterus,	Posterior uterus,
Recto-sigmoid colon,	Recto-sigmoid colon,
Posterior cul de sac,	Posterior cul de sac
Right pelvic side-wall,	Right pelvic side-wall,
Left pelvic side-wall,	Left pelvic side-wall,
Medial right ovary	Medial right ovary
Lateral right ovary	Lateral right ovary
Medial left ovary	Medial left ovary
Lateral left ovary	Lateral left ovary
Right ovarian fossa / posterior broad ligament,	Right ovarian fossa / posterior broad ligament,
Left ovarian fossa / posterior broad ligament,	Left ovarian fossa / posterior broad ligament,
Right tube and fimbria,	Right tube
	Right ampulla
Left tube and fimbria,	Left tube
	Left ampulla

*Extent of adhesion was assigned a moderate score if an adhesion was present.

The American Fertility Society (AFS) scoring system is a method of scoring adhesions at the tube and ovary described by The American Fertility Society (Fertility and Sterility, vol. 49, No. 6, June 1988). A score of 0 to 16 score is determined as per schema below (Table 4), per tube and per ovary on each side: four scores are determined per patient. The scores per anatomic side are added and the lower score per side determines the final AFS score per patient. As each anatomic site, tube / ovary, may score 0 to 16, and as the scores per side are added and only the side with the lower score is reported, the possible AFS score range is 0–32.

Table 4: American Fertility Score (AFS)

AFS Score per site	Severity	Extent
0	None	none
1	Mild	localized
2	Mild	moderate
4	Mild	extensive
4	Severe	localized
8	Severe	moderate
16	Severe	extensive

The INTERGEL pivotal clinical study adhesion score was determined by applying the per site AFS score to each of twenty-four abdomino-pelvic sites, adding the scores of all

twenty four sites (no scores dropped) and normalizing (dividing) by the number of sites.: the possible mAFS score range per patient being 0–16. Extent of adhesion was planned to be assigned a moderate score (1/3 to 2/3) for the anterior peritoneum, small bowel, omentum and large bowel if an adhesion was present due to anticipated difficulty in visualization and/or size. A total adhesion score per patient was calculated, referred to as the modified AFS (mAFS) score.

The standard AFS score was not a prospectively specified parameter of adhesion evaluation and was not determined during clinical study evaluations. However, an AFS score was calculated from mAFS score data using three sites for each ovary and two sites for each tube; the higher score of the right and left side was dropped; the lower score of the right and left side per patient became the AFS score per patient. Further analyses included shift tables in which the calculated AFS were stratified into segments and the shift from baseline to second look was tabulated. The strata included calculated AFS scores (range = 0 – 32) as indicated in Table 5:

Table 5: Stratified AFS Scores

AFS Strata	Score
Minimal	0 – 5
Mild	6 – 10
Moderate	11 – 20
Severe	21 -32
Minimal / mild	0 –10
Moderate / severe	11 – 32

PATIENT ACCOUNTING AND DEMOGRAPHICS

The study was conducted at 11 US Centers and 5 European Centers. The study enrolled 281 patients and 265 patients comprise the evaluable patient population for which a second look effectiveness assessment was performed. Therefore, 281 patients were available for safety data and 265 were evaluable for effectiveness. Table 6 provides the patient accounting and demographics for the pivotal study:

Table 6: Pivotal Study Patient Accounting and Demographics

	Intergel	Control
# treated	143	138
# with no second-look	12*	4
# completed study	131	134
Demographics:		
Race, n (%)		
Caucasian	74 (56.5)	82 (61.2)
Black	28 (21.4)	23 (17.2)
Oriental	4 (3.1)	4 (3.0)
Hispanic	20 (15.3)	22 (16.4)
Other	5 (3.8)	3 (2.2)
Age, mean, sd	33.8 (5.8)	34.2 (5.4)
Weight, mean, sd	150.1 (30.9)	150.2 (31.8)
Baseline Adhesion #, mean (0-24)	3.65	3.46
Baseline mAFS, mean (0-16)	1.07	1.07
Blood loss (cc), mean (sd)	214 (214)	224 (284)
Operative Time (hrs), mean (sd)	1.86 (0.82)	1.80 (0.85)
Days to Discharge, mean (sd)	3.0 (1.6)	3.0 (1.7)
Days to second look, mean (sd)	60.4 (26.2)	58.7 (21.4)

*1 patient was lost to follow-up

ANALYSIS AND RESULTS

The results for the primary effectiveness endpoint, mean mAFS, are presented below in Table 7.

Table 7: Primary Effectiveness Results, Mean mAFS (Range 0-16)

	Intergel	Control	p-value
N	131	134	
Baseline Score (Range 0-16)	1.07	1.07	0.870
2nd Look Score (Range 0-16)	1.36	2.32	0.002

Baseline mean mAFS scores for the Intergel and Control Group were statistically comparable (p=0.870), however, the second look mean mAFS for Intergel was statistically significantly lower than the control (p=0.002).

The secondary effectiveness outcomes are the mean incidence of adhesions (range of 0-24), extent of adhesions (range of 0-3) and severity of adhesions (range of 0-3). These baseline and second look laparoscopy results are provided in Table 8 below.

Table 8: Secondary Effectiveness Results

	Intergel	Control	p-value
N	131	134	
Baseline Incidence (Range 0-24)	3.65	3.46	0.744
2nd Look Incidence (Range 0-24)	6.56	7.63	0.096
Baseline Extent (Range 0-3)	0.29	0.30	0.964
2nd Look Extent (Range 0-3)	0.47	0.63	0.019
Baseline Severity (Range 0-3)	0.38	0.35	0.670
2nd Look Severity (Range 0-3)	0.52	0.73	0.007

AFS SCORE

The effect that treatment had on the stratified AFS score is analyzed in Table 9 below.

Table 9: Shift Table of Baseline and 2nd Look Stratified AFS Score

AFS Category Analysis		INTERGEL® Solution					Lactated Ringer's Solution					
			Second Look					Second Look				
		Baseline Total	Min. 0-5	Mild 6-10	Mod. 11-20	Sev. 21-32	Baseline Total	Min. 0-5	Mild 6-10	Mod. 11-20	Sev. 21-32	p
Minimal	0-5	109	103	4	1	1	109	96	6	3	4	
Mild	6-10	13	10	2	1	0	8	4	1	2	1	
Moderate	11-20	7	6	1	0	0	13	3	4	5	1	
Severe	21-32	2	2	0	0	0	4	2	1	0	1	
Total Second-look		131	121	7	2	1	134	105	12	10	7	0.001* 0.001**

Binary Analysis			Second Look			Second Look		
		Baseline Total	Min./Mild 0-10	Mod./Sev. 11-32	Baseline Total	Min./Mild 0-10	Mod./Sev. 11-32	p
Min./Mild	0-10	122	119	3	117	107	10	
Mod./Sev.	11-32	9	9	0	17	10	7	
Total Second Look		131	128	3	134	117	17	0.003
Relative Risk		(INTERGEL® Solution/Control): 0.195 95% CI: 0.065 to 0.583						

* p value determined using CMH test controlling for Baseline level (ridit scores)
**p value determined using CMH test controlling for Baseline level (median scores)

Analysis using the Cochran-Mantel-Haenszel test controlling for baseline level indicates a statistically significant p value (p=0.001) between treatment groups in the shift from one AFS adhesion category to another. Combining the minimal and mild categories, and the moderate and severe categories (binary analysis), at second-look there were 3 of 131 patients (2.3%) in the moderate/severe category compared to 17 of 134 control patients (12.7%; RR=0.195).

SAFETY

Sixteen (11.2%) patients treated with GYNECARE INTERGEL Solution and seven patients (4.9%) treated with lactated Ringer's solution experienced adverse events considered by the investigator to be possibly, probably, or definitely related to treatment. These events included abdominal and/or post-operative pain, fever, nausea, and constipation, and all resolved spontaneously or with treatment. Treatment-related serious adverse events were experienced by three patients in the GYNECARE INTERGEL Solution group (two cases of abdominal pain, one case of fever) and one patient in the lactated Ringer's solution group (fever). Of the three patients treated with GYNECARE INTERGEL Solution, one required rehospitalization and a diagnostic laparoscopy. All three of these patients had a prolonged hospital stay and received additional medications to resolve their symptoms. The control group patient had a prolonged hospitalization and was treated with medication to resolve her fever. There were no discontinuations due to an adverse event and no deaths occurred during the study.

There were 10 Intergel patients and 4 control patients reported to have infection in the study. Table 10 reports each of these patients and reports the event and whether the investigator assessed the infection to be related to the use of the device.

Table 10: Patients reported as having an infection

Adverse Event	Related to device, Investigator
Intergel Solution Treated Patients (n=143)	
Chicken pox	No
Pelvis infection	No
Bladder pain, infection	Possibly
Klebsiella wound infection, abdominal pain	Possibly
Post-operative Infection	No
Peritoneal fluid culture positive	No
Wound abscess	No
Head cold	No
Vaginal fungal infection*	No
Infection*	Possibly
Lactated Ringer's Solution Treated Patients (n=138)	
Surgical site wound infection	Possibly
Infection	No
Wound infection*	No
Vaginal mycosis*	No

*European patient

The white blood cell analyses indicated a small, but statistically significant increase in neutrophils on postoperative day 3 and day 7-28 and in lymphocytes on postoperative day 3, day 7-8, and at second look laparoscopy for patients treated with GYNECARE INTERGEL Solution compared to patients treated with lactated Ringer's solution.

XI. PANEL RECOMMENDATIONS

On January 12, 2000, the General and Plastic Surgery Devices Panel recommended that this PMA was not approvable. The panel stated the data did not provide a reasonable assurance the device was safe and effective. The panel stated there were concerns regarding the safety of GYNECARE INTERGEL Adhesion Prevention Solution in regards to the potential contribution of the device to the infection rate. Also, the panel stated the number, severity, and extent of adhesions was not clinically different between the treatment and control patients.

On June 2, 2000, the sponsor amended the PMA with a modified indications for use for conservative gynecologic pelvic surgery. On November 15, 2000, the agency found the PMA not approvable because it did not provide reasonable assurance that the product was safe and effective. On January 4, 2001, the sponsor requested that the PMA be reviewed by the Medical Devices Dispute Resolution Panel. On September 6, 2001, the Medical Device Dispute Resolution Panel reviewed the information in the PMA.

The issue discussed most by the Medical Device Dispute Resolution Panel was whether the benefit shown for Intergel was clinically important. In questioning both parties, the Panel was particularly interested in how treatment affected the proportion of patients with moderate/severe adnexal adhesions at second look. The Panel understood that the percentage of individuals with moderate/severe AFS scores at second look had uncertain value in predicting "hard" outcomes of interest (pain, fertility, bowel obstruction). Nevertheless, they understood that the AFS score probably was the best measure, given the constraints of what is feasible, for a prospective clinical trial.

The Medical Device Dispute Resolution Panel had fewer questions about the safety of Intergel and discounted the importance of the trend that suggested a slightly higher infection risk for those receiving Intergel.

The Medical Device Dispute Resolution Panel recommended that this PMA be approved without conditions. The Panel stated that Intergel showed a statistically significant benefit over the lactated Ringer's solution control, and that this evidence was sufficient for approval. Several members did note that the benefit for Intergel was probably modest clinically, but better than no therapy.

XIII. CDRH DECISION

Expedited processing was authorized on April 26, 1999, based on the potential of GYNECARE INTERGEL to provide a specific public health benefit by reducing the incidence, extent, and severity of newly formed adhesions.

Inspection of the Lifecore Biomedical, Inc. manufacturing facilities was completed on December 28, 1999 and January 14, 2000 and was found to be in compliance with the device Quality Systems Regulation.

CDRH carefully considered the discussions and recommendations of both the General and Plastic Surgery Devices Panel and the Medical Device Dispute Resolution Panels. CDRH concluded that the data gathered on the use of the GYNECARE INTERGEL Solution are clinically meaningful and that the data demonstrate that the benefits of the device outweigh the risks, including the risk of infection. Therefore, the data contained in this submission provide reasonable assurance of the safety and effectiveness of GYNECARE INTERGEL Solution for its intended use as an intraperitoneal instillate for reduction of adhesions following gynecological pelvic surgery.

FDA issued an approval order on November 16, 2001.

XIV. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling.

Hazard to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Reactions in the labeling.

Postapproval Requirements and Restrictions: see the Approval Order.